

General

Guideline Title

Guideline for the laboratory diagnosis of functional iron deficiency.

Bibliographic Source(s)

Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I, British Committee for Standards in Haematology. Guideline for the laboratory diagnosis of functional iron deficiency. Br J Haematol. 2013 Jun;161(5):639-48. [76 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Variables for the Assessment of Functional Iron Deficiency or Iron-Restricted Erythropoiesis

Red Cell Variables

- Mean cell volume (MCV) and mean cell haemoglobin (MCH) values are useful at diagnosis and in assessing trends over periods of weeks or months. They have no use in assessing acute changes in iron availability secondary to therapy with erythropoiesis-stimulating agents (ESAs). (1B)
- The percentage of hypochromic red cells (%HRC) is the best-established variable for the identification of functional iron deficiency (FID) and thus has the greatest level of evidence. Reticulocyte haemoglobin content (CHr) is the next most established option. Both tests have limitations in terms of sample stability or equipment availability. Other parameters may be as good but there is no evidence that they are any better, and generally there is less evidence for newer red cell and reticulocyte parameters. (1B)
- A CHr value <29 pg predicts FID in patients receiving ESA therapy. A reticulocyte haemoglobin equivalent (Ret-He) value <25 pg is suggestive of classical iron deficiency and also predicts FID in those receiving ESA therapy. (1B) A Ret-He value <30.6 pg appears to have the best predictive value for likelihood of response to intravenous iron therapy in chronic kidney disease (CKD) patients on haemodialysis. (1B)
- The measurement of red cell zinc protoporphyrin concentration provides a sensitive index of FID and may be used as an alternative to indices of red blood cell (RBC) hypochromia or reticulocyte haemoglobin content, although it is less sensitive than these to acute changes in iron availability. If used in the assessment of FID in CKD patients it is essential that measurements be made on washed cells, with the use of appropriate reference limits. (1B)

Assessment of Iron Stores

Cytological Assessment of Iron Stores

- Bone marrow examination for the sole purpose of assessing iron stores is rarely justifiable. It may be helpful if there are concerns that a high serum ferritin value ($>1200 \mu\text{g/l}$) is not a true reflection of the bone marrow iron storage pool. (1B)

Serum Ferritin

- The serum ferritin assay is essential in the assessment and management of patients with all forms of iron-restricted erythropoiesis (IRE) including FID. Values $<12 \mu\text{g/l}$ indicate absent iron stores. (1A) Values as high as $1200 \mu\text{g/l}$ in CKD patients do not exclude the possibility of FID and some such patients may respond to intravenous iron therapy. No recommendation as to the highest serum ferritin concentration beyond which it is unsafe to give a trial of intravenous iron therapy can be given. A serum ferritin concentration $<100 \mu\text{g/l}$ in nondialysed patients or $<200 \mu\text{g/l}$ in chronic haemodialysis patients is associated with a high likelihood of iron deficiency and a potentially good response to intravenous iron therapy. (1A) Values above the suggested cut-offs given above should therefore not be used to guide iron therapy. Serum ferritin values $>1200 \mu\text{g/l}$ should be used to ascertain whether investigation of potential iron overload should be undertaken. (1B)
- The serum ferritin concentration is not useful in predicting ESA responsiveness in cancer-related anaemia (1A)

Soluble Transferrin Receptor

- The soluble transferrin receptor (sTfR) assay is relatively expensive, not widely available, and is not currently subject to external quality assessment (EQA) in the UK. An International Standard may improve assay standardization. The treatment of renal anaemia with ESAs, which increase sTfR, is a complicating factor. The assay may have a role, either alone or in combination with the ferritin assay, if automated measures such as %HRC, CHr or Ret-He are unavailable. (1B)

Serum Iron, Total Iron-Binding Capacity (TIBC) and %Saturation (%Sat)

- In isolation the percentage saturation of transferrin is not recommended as a predictor of responsiveness to intravenous iron therapy in patients with CKD. It may be used to monitor response to ESA and/or iron therapy in CKD. It may be used to monitor response to ESA and/or iron in CKD. When used with either the serum ferritin concentration or measurement such as %HRC and CHr it may be useful in the diagnosis of FID. (1A)

Erythropoietin

The measurement of serum erythropoietin concentration in the setting of anaemia has limited value in the diagnosis of FID. (1A)

Hepcidin

- The utility of hepcidin measurement as a diagnostic tool is currently uncertain and for the time being this technique remains a research investigation.

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context, it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

An algorithm for management of iron-restricted erythropoiesis in patients with chronic kidney disease (CKD) on erythropoiesis-stimulating agents (ESAs) is provided in the original guideline document.

Scope

Disease/Condition(s)

- Functional iron deficiency (FID)
- Anaemia of chronic disease (ACD)
- Chronic kidney disease (CKD)

Note: FID is a state in which there is insufficient iron incorporation into erythroid precursors in the face of apparently adequate body iron stores. FID is a major component of the anaemia of chronic disease (ACD).

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Family Practice

Hematology

Internal Medicine

Nephrology

Oncology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals with clear guidance on the management of functional iron deficiency (FID), in particular with respect to patients with chronic kidney disease (CKD), but also to other disease states in which erythropoietin-stimulating agents (ESAs) have been used

Target Population

Adult patients with chronic kidney disease (CKD) or other disease states in which erythropoiesis-stimulating agents (ESAs) have been used

Note: The guidance may not be appropriate to patients with inflammatory diseases and in all cases individual patient circumstances may dictate an alternative approach. This guideline is only applicable to adults, not children.

Interventions and Practices Considered

1. Mean cell volume (MCV) and mean cell haemoglobin (MCH) values
2. Percentage of hypochromic red cells (% HRC)
3. Reticulocyte haemoglobin content (CHr)
4. Red cell zinc protoporphyrin concentration
5. Serum ferritin assay
6. Soluble transferrin receptor (sTfR) assay
7. Percentage saturation of transferrin
8. Serum erythropoietin concentration

Major Outcomes Considered

- Sensitivity and specificity of tests for assessment of iron
- Inadequate iron supply
- Iron overload
- Effects of, or need for, supplementation with iron or erythropoiesis-stimulating agents (ESAs)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

MEDLINE was searched systematically for publications in English from 1966-2011 using key words: functional iron deficiency and each of the parameters discussed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context, it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline group was selected to be representative of United Kingdom (UK)-based experts in the clinical and laboratory fields of iron metabolism, chronic kidney disease (CKD), quality control and method evaluation.

The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Task Force of the British Committee for Standards in Haematology (BCSH).

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of United Kingdom (UK) haematologists and members of both the British Committee for Standards in Haematology (BCSH) and the British Society for Haematology. Comments were incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of functional iron deficiency (FID) in patients with chronic kidney disease (CKD) or other disease states in which erythropoiesis-stimulating agents (ESAs) have been used

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.
- The guidance may not be appropriate to patients with inflammatory diseases and in all cases individual patient circumstances may dictate an alternative approach. This guideline is only applicable to adults, not children.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Jun

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology Writing Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [British Committee for Standards in Haematology Web site](#) .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on June 21, 2013.

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